

## Patient Safety Tip of the Week

March 25, 2014

### Melatonin and Delirium

We've done numerous columns on recognition, prevention, and management of delirium (see list at the end of today's column). Pharmacological interventions to prevent delirium have been disappointing. The most successful interventions have been multimodality ones and, even then, benefits have been modest. One of the mainstays of those multimodality interventions has been the attempt to maintain sleep-waking cycles as close to normal as possible. So it was only a matter of time until someone would attempt to use melatonin, the pineal gland hormone important in regulation of sleep-waking cycles, to prevent delirium.

There have been a few old studies and a new study looking at melatonin as a potential intervention to prevent delirium in hospitalized patients.

In a study of 300 elderly patients undergoing hip arthroplasty, Sultan ([Sultan 2010](#)) randomized patients to 4 arms of sedation (none, melatonin, midazolam, and clonidine). Only 9.4% of patients in the melatonin arm developed post-op delirium, compared to 32.7% of those in the control arm. In addition, 58% of those who developed post-op delirium were successfully treated with melatonin.

Another small (n = 145) randomized controlled study evaluated low dose melatonin in elderly patients admitted to an acute medical service ([Al-Aama 2011](#)) found that melatonin was associated with a lower risk of delirium (12.0% vs. 31.0%).

In the new study Hatta and colleagues did a multicenter randomized controlled trial of ramelteon, a melatonin agonist, in elderly patients in ICU's and acute care wards to see if it could prevent delirium ([Hatta 2014](#)). Patients were 69-89 years old, were admitted for acute medical problems, had an expected length of stay and life expectancy longer than 48 hours, and had to be able to take oral medications. Patients on certain medications or with certain other conditions were also excluded. In fact, of 1126 patients assessed for eligibility, 1059 were excluded. Ultimately, 67 patients were randomized to receive either placebo or ramelteon.

Ramelteon was associated with a lower risk of delirium (3% vs 32%; p =0.003), with a relative risk of 0.09. Even after risk factors were controlled for, ramelteon was still

associated with a lower incidence of delirium (odds ratio 0.07). Interestingly, though the difference in delirium incidence was great, measured sleep parameters did not differ between those in the two study arms.

Though the number of patients in this study met the authors' power analysis, its conclusions are limited by the fact that this is a very small sample size. The study was also not double-blinded. The raters were blinded but patients were not and the placebo apparently differed in appearance from the active medication. There was also substantial cessation of medication before the planned 7 days in both arms. And the huge number of excluded patients is of concern.

Call us skeptics when it comes to all 3 of these studies. We are of the John Ioannidis school of thought that says "if it sounds too good to be true, it probably is not true" ([Ioannidis 2005](#), [Pereira 2012](#)). Those authors conclude that most large treatment effects emerge from small studies, and when additional trials are performed, the effect sizes become typically much smaller.

So don't run out and start treating your at-risk patients with melatonin or melatonin agonists yet. Nevertheless, given the serious implications of delirium and our currently limited interventions to prevent it, these studies pose a hypothesis that should be tested in well-designed randomized controlled trials. Stay tuned.

#### **Some of our prior columns on delirium assessment and management:**

- October 21, 2008 "[Preventing Delirium](#)"
- October 14, 2009 "[Managing Delirium](#)"
- February 10, 2009 "[Sedation in the ICU: The Dexmedetomidine Study](#)"
- March 31, 2009 "[Screening Patients for Risk of Delirium](#)"
- June 23, 2009 "[More on Delirium in the ICU](#)"
- January 26, 2010 "[Preventing Postoperative Delirium](#)"
- August 31, 2010 "[Postoperative Delirium](#)"
- September 2011 "[Modified HELP Helps Outcomes in Elderly Undergoing Abdominal Surgery](#)"
- December 2010 "[The ABCDE Bundle](#)"
- February 28, 2012 "[AACN Practice Alert on Delirium in Critical Care](#)"
- April 3, 2012 "[New Risk for Postoperative Delirium: Obstructive Sleep Apnea](#)"
- August 7, 2012 "[Cognition, Post-Op Delirium, and Post-Op Outcomes](#)"
- September 2013 "[Disappointing Results in Delirium](#)"
- October 29, 2013 "[PAD: The Pain, Agitation, and Delirium Care Bundle](#)"
- February 2014 "[New Studies on Delirium](#)"

#### **References:**

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